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- (71) Applicant (*for all designated States except US*): BIO-CHEMIE GESELLSCHAFT M.B.H. [AT/AT]; A-6250 Kundl (AT).



(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GREIL, Julia [AT/AT]; Brandenberger Strasse 1, A-6233 Kramstach (AT). LUDESCHER, Johannes [AT/AT]; Kleinsöll 101, A-6252 Breitenbach (AT). WOLF, Siegfried [AT/AT]; Judenwiese 4a, 6230 Brixlegg (AT).

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(54) Title: INTERMEDIATES IN CEPHALOSPORIN PRODUCTION

(57) Abstract: A salt of PACA with an amidine and its use in the production of cefprozil.

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Intermediates in cephalosporin production

The present invention relates to intermediates in cephalosporin production.

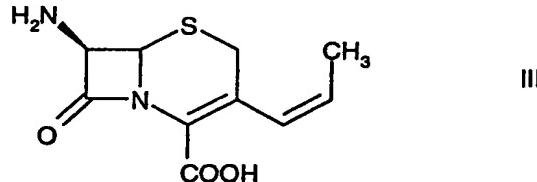
Cefprozil [6R-[6 α ,7 β (R*)]-7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-(1-propenyl)-3-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, e.g. in the form of a monohydrate (see

5 e.g. The Merck Index, 12th edition, item 1992), is a broadly used cephalosporin antibiotic.

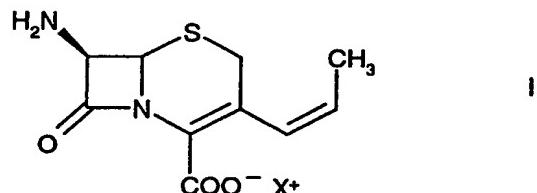
We have now found a simple and economic process, e.g. useful on technical scale; for the production of cefprozil, e.g. in the form of a monohydrate, e.g. in pure form.

In one aspect the present invention provides a process for the production of cefprozil, e.g.

10 in the form of a solvate, e.g. hydrate, such as a monohydrate, comprising the steps
A1) reacting PACA of formula

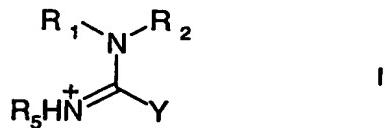


In the form of a salt with an amidine, e.g. a compound of formula



15 wherein

X⁺ is a group of formula



and either

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- a) Y is a group of formula -NR₃R₄ and
 - a1) R₁ to R₅ are the same or different and are independently of each other hydrogen, alkyl or aryl; or
 - a2) two of the substituents R₁, R₂ and R₅, and/or R₃ and R₄ together form a -(CH₂)₂- or -(CH₂)₃- group; and the other substituents R₁ to R₅ are as defined above; or
 - b) Y forms together with R₂ a -(CH₂)₃- or -(CH₂)₅- group, and R₁ and R₅ together form a -(CH₂)₃- group,
 - with a mixed carboxylic acid anhydride of an α-amino-p-hydroxyphenylacetic acid, and
- 5 B1) isolating cefprozil from the reaction mixture obtained in step A1); and optionally
- 10 C1) converting cefprozil isolated in step B1) into cefprozil in the form of a monohydrate.

In another aspect the present invention provides a process for the production of cefprozil, e.g. in the form of a solvate, e.g. N,N-dimethylformamide (DMF) solvate (e.g. cefprozil x1.5
15 DMF) or hydrate, e.g. monohydrate, which comprises the steps

A2) producing a mixed carboxylic acid anhydride by acylating a vinyl substituted α-amino-p-hydroxyphenylacetic acid with an appropriate acylating agent,

B2) reacting a mixed carboxylic acid anhydride obtainable in step A2) with PACA in the form of a salt with an amidine, e.g. a compound of formula I wherien X⁺ is as defined
20 above,

C2) isolating cefprozil, e.g. in the form of a solvate, e.g. N,N-dimethylformamide solvate, e.g. in crystalline form; obtained in step B2), and optionally

D2) converting cefprozil obtained in step C2), e.g. in the form of an N,N-dimethylformamide solvate; into cefprozil in the form of a hydrate; e.g. a monohydrate.

25 A process according to the present invention may be carried out as appropriate, e.g. according to, e.g. analogously, to a method as conventional, and is preferably carried out as follows:

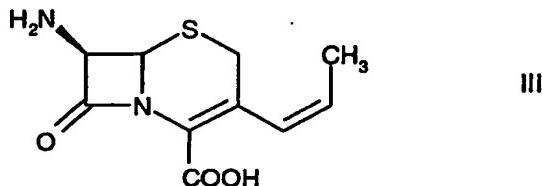
Step A1), or step B2), respectively, is an acylation reaction with a mixed carboxylic acid anhydride.

30 An appropriate mixed carboxylic acid anhydride is preferably provided according to step A2), i.e. by acylating, e.g. reacting, an N-vinyl substituted α-amino-p-hydroxyphenylacetic acid, with an appropriate acylating agent. For that acylation the N-substituted vinyl α-amino-

- p-hydroxyphenylacetic acid may be used in free form or in the form of a salt, e.g. including a Dane salt, such as sodium or potassium D-N-(1-methoxycarbonylpropen-2-yl)- α -amino-p-hydroxyphenylacetate, or sodium or potassium D-N-(1-ethoxycarbonyl-propen-2-yl)- α -amino-p-hydroxyphenylacetate. Appropriate acylating agents include aliphatic, alicyclic, or
- 5 aromatic acids, e.g. including alkanoic acids, such as chloroformic acid, pivalic acid, 2-ethylhexanoic acid, benzoic acid, e.g. in a reactive form. A reactive form includes acid halogenides, e.g. chlorides, e.g. including pivaloyl chloride, 2-ethyl-hexanoyl chloride, benzoyl chloride and esters, e.g. chloroformic acid alkyl esters, such as ethyl chloroformate. In step A2) a small amount of a free C₄-C₉ acid may be present, e.g. an alkanoic acid such
- 10 as pivalic acid or 2-ethylhexanoic acid, or an aromatic acid, e.g. benzoic acid, preferably 2-ethylhexanoic acid or pivalic acid, e.g. which may catalyze the mixed carboxylic acid anhydride formation. The side chain of said free carboxylic acid may be the same or different to that of the acylating agent and is preferably the same. Appropriate solvents in step A2) include halogenated hydrocarbons e.g dichloromethane or acetic acid (C₁,
- 15 alkylesters such as butylacetate or isopropylacetate. A co-solvent may be present which may improve or activate the reaction of above Dane salts with the acylating agent, such as organic amides, e.g. in the form of N-substituted amides, e.g. including formamide, acetamides, N-mono or N,N-dimethyl amides, such as N,N-dimethyl formamide (DMF), N-methylacetamide, N,N-dimethylacetamide; pyrrolidines, such as N-methylpyrrolidines;
- 20 uréas, e.g. tetramethylurea, branched chain alkyl alcohols, such as isopropanol; preferably DMF. Preferably a base, e.g. a tertiary amine base, may be present as a catalyst in step A2). A preferred base includes pyridines, for example a picoline, e.g. 3- or 4-picoline, or a lutidine. The formation of the mixed carboxylic acid anhydride in step A2) may be effected at temperatures as appropriate, e.g. including temperatures from -50° to 50°C, preferably
- 25 from -40°C to 0°C. A solution or a suspension of a mixed carboxylic acid anhydride may be obtained which may be used further, e.g. in step A1) or B2), as such, e.g. without isolation of the mixed carboxylic acid anhydride, e.g. which solution or a suspension may be stored, e.g. at appropriate temperatures, e.g. including temperatures from (ca.) -60°C to -20°C.
- 30 Step A1), or, step B2), respectively, is an acylation reaction of the amine group of a PACA-amidine with a mixed carboxylic acid anhydride, e.g. obtainable according to step A2). PACA in the form of a salt with an amidine, e.g. a compound of formula I, wherein X⁺ is as defined above, is novel.

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In another aspect the present invention provides PACA of formula



In the form of a salt with an amidine, e.g. a compound of formula I as defined above wherein X⁺ is as defined above, e.g. in the form of an acid addition salt or in the form of a

- 5 solvate of a compound of formula I or in the form of a solvate of an acid addition salt of a compound of formula I.

In another aspect the present invention provides the use of a compound according to the present invention, e.g. as an intermediate, in the production of cefprozil.

10

PACA in the form of a salt(s) with an amidine according to the present invention is hereinafter designated as "PACA-amidine(s)".

PACA-amidines may exist in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate. PACA-amidines in free form may be converted into PACA-amidines in the form of a salt and vice versa. PACA-amidines in the form of a solvate or in the form of a salt and a solvate may be converted into PACA-amidines in unsolvated form or PACA-amidines in the form of a salt in unsolvated form and vice versa.

PACA-amidines are e.g. useful in a process for the production of cefprozil according to the present invention and may be stable soluble forms of PACA in a solvent or solvent mixtures

- 20 which may allow further reacting, e.g. acylating the amine group in position 7 of the ring structure, easily, e.g. without the need to solubilize PACA either by silylation or the use of complex solvent mixtures. PACA-amidines may be stable despite the high basicity of the corresponding bases, e.g. with respect to degradation and with respect to Z/E isomerization; and additionally may be soluble in a number of solvents or solvent mixtures
- 25 and may thus allow to choose solvents or solvent mixtures in a further reaction step, which easily may be recycled from a reaction mixture obtained in said further reaction step, e.g. in a process for the production of cefprozil.

PACA-amidines include PACA amidine salts and guanidine salts, which guanidines being amino-amidines, having an amidine structure and carrying a further amine group at the

- 30 carbon atom of the -N=C-N-group. Appropriate guanidine salts include e.g. compounds of

formula II, wherein Y denotes a group of formula $-NR_3R_4$ wherein R₃ and R₄ are as -defined above.

If not otherwise defined herein any carbon atom containing group preferably may contain up to 20 carbon atoms. Aryl includes phenyl, naphthyl. Any group may be unsubstituted or

- 5 substituted, e.g. substituted as appropriate, e.g. according, e.g. analogously, as conventional in organic chemistry, e.g. β -lactam chemistry, such as cephalosporin chemistry. A solvent includes a solvent mixture (system) of individual solvents, e.g. as correspondingly indicated.

In a compound of formula II preferably Y is a group of formula $-NR_3R_4$ and R₁ to R₅ are

- 10 independently of each other hydrogen, unsubstituted alkyl or alkyl substituted by a phenyl group, for example benzyl, or unsubstituted aryl; preferably R₁, R₂, R₃ and R₄ are (C₁₋₄)alkyl and R₅ is hydrogen; or Y together with R₂ form a -(CH₂)₃- or -(CH₂)₅- group, and R₁ and R₅ together form a -(CH₂)₃- group. Preferred PACA-amidines include PACA in the form of a salt with tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-
- 15 diazabicyclo[4.3.0]non-5-ene (DBN).

The production of a PACA-amidine salt is a salt formation process which may be carried out as appropriate, and is preferably carried out as follows:

PACA may be suspended in an appropriate solvent and an amidine is added. An appropriate solvent system is described below for providing a solution of a PACA-amidine.

- 20 A solution may be obtained, e.g. if PACA is in the form of a salt with a guanidine which guanidine is in the form of a free base. The ratio of PACA and an amidine is not critical. E.g. per equivalent PACA 1 to 2, e.g. 1 to 1.5, preferably 1 to 1.2 equivalents of an amidine may be used. From the mixture obtained a PACA-amidine may be isolated in the form of a solid, e.g. an amorphous powder, foam, e.g. solvent may be evaporated off and the evaporation residue may be treated with an anti-solvent. An anti-solvent is a solvent wherein a PACA-
- 25 amidine is less soluble than in a solvent, e.g. including ethers, e.g. tert. butyl-methylether, diethylether, or hydrocarbons, e.g. hexane. A PACA-amidine may be isolated as appropriate, e.g. by solvent decantation or filtration.

- An appropriate solvent system for providing a solution of a PACA-amidine and for providing
30 PACA-amidines includes e.g. halogenated hydrocarbons, preferably dichloromethane, alkanols, e.g. (C₁₋₄) alkanols, such as ethanol, butanol, isopropanol, preferably a (C₃₋₄)alkanol, such as butanol, for example n-butanol, iso-butanol, tert.-butanol or sec.-butanol, or isopropanol, e.g. isopropanol; optionally in combination with a solvent as described above in step A2). Optionally water may be present.

In another aspect the present invention provides a process for the production of PACA in the form of a salt with an amidine comprising suspending PACA of formula III in an appropriate solvent, adding an amidine and isolating PACA in the form of a salt with an
5 amidine.

For carrying out step A1), or, step B2), respectively, conveniently a solution of a PACA-amidine, e.g. obtainable as described above, may be reacted with, e.g. may be added to, a reaction mixture comprising a mixed carboxylic acid anhydride, e.g. obtainable according to
10 step A2). If desired a small amount of water may be present in the solvent (system). If desired a small amount of a (C₄₋₉)alkanoic acid, e.g. including 2-ethylhexanoic acid, may be added to a mixture of a PACA-amidine and solvent (system). Appropriate reaction temperatures include e.g. about -60°C to room temperature, preferably -50°C to -15°C. Cefprozil, e.g. in a protected form, may be obtained. Cefprozil in a protected form e.g.
15 includes cefprozil, wherein the amine group of the glycyl group attached to the amine group in position 7 of the ring structure, is protected by a substituted vinyl group, e.g. according to a Dane salt used in the production of a mixed anhydride, e.g. as described above in step A2.
If cefprozil is obtained in a protected form cefprozil may be deprotected, e.g. a substituted
20 vinyl group may be split off as appropriate, e.g. by hydrolysis in aqueous acid. Cefprozil may be obtained and may be isolated.

Step B1), or C2), respectively, i.e. the isolation of cefprozil, may be carried out as appropriate and is preferably carried out as follows:

25 The reaction mixture obtained in step A1) or B2), respectively, may be worked up as appropriate and cefprozil may be isolated as appropriate, e.g. according, e.g. analogously, to a method as conventional. Cefprozil is preferably isolated in the form of a solvate, e.g. in the form of an N,N-dimethylformamide solvate (1/1.5), e.g. in crystalline form, by crystallization of the N,N-dimethylformamide solvate (DMF-solvate) from aqueous, or
30 aqueous/alkanolic respectively, solution by addition of DMF and pH adjustment within 4.5 to 7. Formation of cefprozil in the form of a DMF-solvate, e.g. in crystalline form, is e.g. described in US 4,694,079 which is introduced herein by reference.

Step C1) or D2), respectively, i.e. conversion of cefprozil, e.g. in the form of a DMF-solvate, into cefprozil in the form of a hydrate, e.g. monohydrate may be carried out as appropriate and is preferably carried out as follows:

Cefprozil, e.g. in the form of an DMF-solvate (e.g. 1/1.5) may be mixed with water and an

- 5 inorganic acid, e.g. hydrochloric acid; e.g. dissolution of cefprozil may be facilitated by addition of said inorganic acid. From the mixture obtained cefprozil in the form of a hydrate, e.g. a monohydrate may be crystallized by addition of an inorganic base, e.g. including sodium hydroxide or aqueous ammonia to adjust a pH which is around the isoelectric point of cefprozil, e.g. at appropriate temperatures, e.g. including temperatures of room
- 10 temperature or above, e.g. room temperature to 60°C, such as 30°C to 50°C. Alternatively cefprozil, e.g. in the form of an DMF-solvate, may be converted into cefprozil in the form of a monohydrate by heating a solution or suspension in water at elevated temperates, e.g. including temperatures of 30°C to 60°C.
- 15 Cefprozil in the form of a hydrate, e.g. monohydrate, e.g. in crystalline form may be isolated from the reaction mixture as appropriate, e.g. by filtration, centrifugation.

In the following examples all temperatures are in degree Centigrade and are uncorrected.

The following abbreviations are used:

- | | |
|-----------------|---|
| DMF: | N,N-dimethylformamide |
| 20 TMG: | tetramethylguanidine |
| DBU: | 1,8-diaza-bicyclo-(5.4.0)undec-7-ene |
| DBN: | 1,5-diaza-bicyclo-(4.3.0)non-5-ene |
| PACA: | a compound of formula III as defined above |
| ETHER: | tert. butyl-methylether |
| 25 DMF-solvate: | cefprozil in the form of a solvate with DMF |

EXAMPLE 1**Production of cefprozil****a) Mixed carboxylic acid anhydride formation**

To a mixture of 78.1 ml of CH₂Cl₂, 49.7 ml of DMF and 0.3 ml of 4-picoline, 30.24 g of

5 potassium D-N-(1-methoxycarbonylpropen-2-yl)- α -amino phenylacetate are added. The suspension obtained is stirred at room temperature and is cooled to -30°. To the mixture obtained 12.42 ml of pivaloylchloride are added and the suspension obtained is stirred at a temperature of -20° to -25°, cooled to -50°C and diluted by addition of 41.8 ml of cold DMF.

10 b) PACA in the form of a salt with TMG

A suspension of 148 ml of CH₂Cl₂ and 20.77 g of PACA is cooled to -10° and 11.43 ml of TMG are added. The suspension obtained is warmed up and a solution is obtained. The solution obtained is cooled to -50°.

c) Acylation reaction of the free amine group in PACA in the form of a salt with TMG

15 The solution obtained in step 1b) is added to the suspension obtained in step 1a) at a rate that the temperature does not exceed -40° and the mixture obtained is stirred at -45° for ca. 1 hour and at -35° for ca. 2 hours. Cefprozil wherein the amine group of the glycyl group attached to the amine group in position 7 of the cephalosporin ring structure is protected by a 1-methoxycarbonylpropen-2-yl group is obtained.

20 d) Cefprozil in the form of a DMF-solvate

The mixture obtained in step 1c) is added to a mixture of 81 ml of ice water and 18 ml of concentrated HCl and the mixture obtained is stirred. Two phases obtained are separated. To the aqueous layer obtained 180 ml of DMF are added and the pH of the mixture obtained is adjusted with 25% aqueous ammonia to 2.5 at a temperature of ca. 30°. To the 25 mixture obtained 44 ml of DMF are added and the pH is adjusted to 4.2 with 25% aqueous ammonia. To the mixture obtained seed crystals of a DMF-solvate, i.e. cefprozil x(1/1.5) DMF solvate are added. Cefprozil in the form of a cefprozil x(1/1.5) DMF solvate crystallizes. The pH of the suspension obtained is adjusted to 6.8 and the suspension is allowed to stand at 30°. Cefprozil in the form of a cefprozil x(1/1.5) DMF solvate in 30 crystalline form is filtrated off, washed and dried.

e) Cefprozil in the form of a monohydrate

56.3 ml of H₂O are heated to 48°. 40 g of cefprozil in the form of a cefprozil x(1/1.5) DMF solvate are added with stirring. The suspension obtained is stirred, slowly cooled down and

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kept at about 5°. Cefprozil in the form of a monohydrate crystallizes, is filtrated off, washed and dried.

EXAMPLE 2

5 PACA in the form of a salt with TMG

12.01 g of PACA are suspended in 120 ml of CH₂Cl₂, the mixture obtained is cooled in an ice bath and 1.1 equivalents of TMG are added. A solution is obtained, concentrated in vacuo and the evaporation residue is treated with ETHER. Solvent is decanted and the decantation residue is dried. PACA in the form of a salt with TMG is obtained in the form of
10 an amorphous powder. ¹H-NMR(CDCl₃, TMS): 1.74 (3H,dd,CH₃ of PACA), 2.97 (12H,s,CH₃ of TMG), 3,36 and 3,62 (1H,AB,S-CH₂-,H-2), 4.62 (1H,d,CH,H-7), 5,00 (1H,d,CH,H-6), 5.52 (1H,dq,=CH-CH₃ of PACA), 6.39 (1H,d(m),CH= of PACA)

EXAMPLE 3

15 PACA in the form of a salt with DBU

12.01 g of PACA are suspended in 120 ml of CH₂Cl₂, the mixture obtained is cooled in an ice bath and 1.1 equivalents of DBU are added. A solution is obtained, concentrated in vacuo, the concentration residue is treated with ETHER, the solvent is decanted and the decantation residue obtained is dried. PACA in the form of a salt with DBU is obtained in
20 the form of an amorphous powder. ¹H-NMR(CDCl₃, TMS): 1.60-1.80 (9H,M, CH₃ PACA, 3 x C-CH₂-C of DBU), 1.99 (2H,Tt,C-CH₂-C of DBU), 2.87 (2H,M,C-CH₂-C of DBU), 3,33-3,64 (8H,M,S-CH₂-, H-2,3 x C-CH₂-N of DBU), 4.62 (1H,D,CH, H-7), 5.01 (1H,D,CH, H-6), 5.55 (1H,d(m), CH=double bonds), 6.39 (1H,Dq,=CH-CH₃)

25 EXAMPLE 4

PACA in the form of a salt with DBN

12.01 g of PACA are suspended in 120 ml of CH₂Cl₂, the mixture obtained is cooled in an ice bath and 1.1 equivalents of DBN are added. A solution is obtained, concentrated in vacuo, the concentration residue is treated with ETHER, solvent is decanted and the
30 decantation residue is dried. PACA in the form of a salt with DBN in the form of an amorphous powder is obtained. ¹H-NMR(CDCl₃, TMS): 1.74 (3H,dd,CH₃ PACA), 2.00 (2H,tt,C-CH₂-C DBN), 2.12 (2H,tt,C-CH₂-C of DBN), 3.10 (2H,t,C-CH₂-C of DBN), 3.37 (2H,t,C-CH₂-N DBN), 3.46 (2H,t, C-CH₂-N DBN), 3.58 (2H,t,C-CH₂-N DBN), 3,36-3,62

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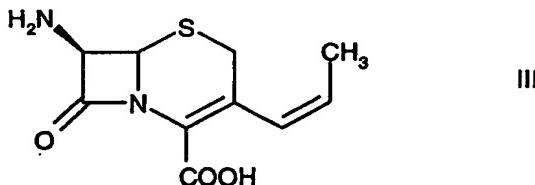
(2H,m,S-CH₂-,H-2), 4.62 (1H,d,CH,H-7), 5.01 (1H,d,CH,H-6), 5.56 (1H,dq,=CH-CH₃ PACA),
6.39 (1H,d(m),CH= PACA)

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Patent claims

1. A process for the production of cefprozil comprising the steps

A1) reacting PACA of formula



5

in the form of a salt with an amidine with a mixed carboxylic acid anhydride of an α -amino-p-hydroxyphenylacetic acid, and

B1) isolating cefprozil from the reaction mixture obtained in step A1); and optionally

C1) converting cefprozil isolated in step B1) into cefprozil in the form of a monohydrate.

10

2. A process for the production of cefprozil in the form of a monohydrate which comprises the steps

A2) producing a mixed carboxylic acid anhydride by acylating a vinyl substituted α -amino-p-hydroxyphenylacetic acid with an appropriate acylating agent,

15

B2) reacting a mixed carboxylic acid anhydride obtainable in step A2) with PACA in the form of a salt with an amidine,

C2) isolating cefprozil, and

D2) converting cefprozil obtained in step C2) into cefprozil in the form of a monohydrate.

20

3. A process according to any one of claims 1 to 2 wherein cefprozil is isolated in the form of a N,N-dimethylformamide solvate (1/1.5).

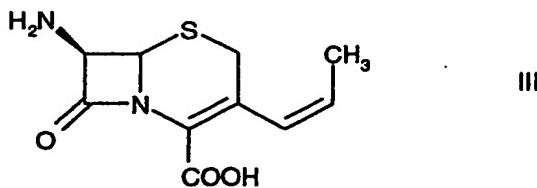
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4. A process according to claim 3 wherein cefprozil in the form of a N,N-

dimethylformamide solvate is converted into cefprozil in the form of a monohydrate.

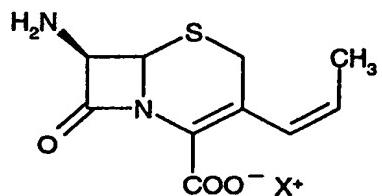
5. PACA of formula:

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in the form of a salt with an amidine.

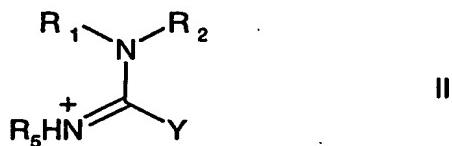
6. A compound according to claim 5 of formula



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wherein

X^+ is a group of formula



Y is

10 a) a group of formula $-NR_3R_4$ and

a1) R_1 to R_5 are the same or different and are independently of each other

hydrogen, alkyl or aryl; or

a2) two of the substituents R_1 , R_2 and R_5 , and/or R_3 and R_4 together form a $-(CH_2)_2-$ or $-(CH_2)_3-$ group; and the other substituents R_1 to R_5 are as defined above; or

15 b) together with R_2 form a $-(CH_2)_3-$ or $-(CH_2)_5-$ group, and R_1 and R_5 together form a $-(CH_2)_3-$ group.

7. A compound of any one of claims 5 or 6 in the form of an acid addition salt.

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8. Use of a compound as claimed in any one of claims 5 to 6 in the production of cefprozil.

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9. A process for the production of PACA of formula III as defined in claim 3, in the form of a salt with an amidine comprising suspending PACA of formula III in appropriate solvent, adding an amidine and isolating PACA in the form of a salt with an amidine.
- 5 10. A process, a compound or the use of any preceding claim, wherein PACA in the form of a salt with an amidine is selected from the group consisting of a compound of formula III as defined in claim 1 in the form of a salt with tetramethylguanidine, 1,8-diaza-bicyclo-(5.4.0)undec-7-ene or 1,5-diaza-bicyclo-(4.3.0)non-5-ene.

INTERMEDIATES IN CEPHALOSPORIN PRODUCTION

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Inventor(s): GREIL JULIA (AT); WOLF SIEGFRIED (AT); LUDESCHER JOHANNES (AT)

Applicant(s): GREIL JULIA (AT); BIOCHEMIE GMBH (AT); WOLF SIEGFRIED (AT); LUDESCHER JOHANNES (AT)

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Equivalents:

Cited Documents:

Abstract

A salt of PACA with an amidine and its use in the production of cefprozil.

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